

REMARKS

This Reply is responsive to the Office Action dated June 13, 2005. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter are respectfully requested.

Applicants respectfully submit that no prohibited new matter has been introduced by the amendment. Support for the amendments to the claims can be found in the original claims, figures and throughout the specification as originally filed. The table below provides specific written support for the claim amendments and new claims.

Claims	Written Support
Claim 22	Page 9, lines 2-4 Example 4 (page 31) Figure 7 Figure 5 Page 23, lines 10-14
Claim 41	Page 23, lines 4-24
Claim 43	Page 25, lines 2-5 Page 23, lines 10-14
Claim 62	Page 23, lines 4-24
Claim 64	Page 25, lines 13-17 Page 23, lines 10-14
Claim 103	Page 9, lines 2-4 Example 4 (page 31) Figure 7
Claim 104	Page 25, lines 2-5
Claim 105	Page 9, lines 2-4 Page 25, lines 13-17

As amended, claims 22-24, 26, 28-41, 43-45, 47, 49-62, 64-67, 69, 71, 73-82, and claims 103-105 are currently under consideration.

Rejection of claims 22-24, 26, 28-41, 43-45, 47, 49-62, 64-67, 69, 71, and 73-82 under 35 U.S.C. §112, first paragraph

In the Office Action, claims 22-24, 26, 28-41, 43-45, 47, 49-62, 64-67, 69, 71, and 73-82 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement.

The Examiner alleges that claims 22-24, 26, 28-41, 43-45, 47, 49-62, 64-67, 69, 71, and 73-82 are not enabled by the specification because an artisan cannot attribute a measured channel activity to a specific G protein coupled receptor, to the exclusion of all of the other G protein-coupled receptors expressed by a test cell, in the absence of a comparative step that employs a cell that is otherwise identical to the test cell except for the absence of receptor protein of interest. The Examiner acknowledges that the use of a negative control for a G coupled protein receptor was known in the art. However, the Examiner contends that controls are a critical element of the claimed process and that the instant specification does not provide the guidance needed to practice the process without the element.

Applicants respectfully disagree. As acknowledged in the Office Action, the use of GPCR controls is well known in the art. It is well established that Applicants need not disclose that which is well known in order to satisfy the enablement requirement. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). In any case, the application does disclose the use of appropriate controls for the claimed methods. For instance, with regard to the embodiment of claim 22, Example 4 (page 31, lines 14-21) of the specification describes the measurement of fluorescence signals produced by the addition of dopamine, a ligand to dopamine type I receptor, to cells transfected with dopamine type I receptor and a mutated CNG channel. Figure 7, which corresponds to Example 4, is a dose response curve which demonstrates that the amount of fluorescence, *i.e.* the level of activity of the channel and GPCR,

increased as the level of dopamine increased. The dose response curve compares the amount of fluorescence in the absence of ligand (0 μ M dopamine sample) to the presence of ligand (0.003, 0.01, 0.03, 0.1, 0.3, and 1 μ M dopamine samples) over time. Similarly, Figure 5 is a graph of membrane potential as a function of time and shows an increase of fluorescence when 10 μ M of isoproterenol, a ligand for beta-adrenergic receptor, is added to HEK293 cells transiently transfected with a CNG channel, compared to the fluorescence when no isoproterenol is added. It would be clear to the skilled artisan reviewing this disclosure that a suitable control for monitoring the activity of a GPCR receptor in the presence of its known ligand, as covered by claim 22, would be to measure activity in the absence of ligand, as well as to create a dose response curve in the presence of varying concentrations of ligand.

With regard to the embodiment of claim 43, Example 14 (page 38, lines 9-23) describes how a CNG channel assay was used to identify putative GPCR ligands in a panel of adrenergic compounds. The adrenergic test compounds were added 20 seconds after the start of recordings to a final concentration of 1 μ M to transformed HEK293H cells expressing a CNG channel gene. In addition to the 20 second period of time of recorded fluorescence prior to the addition of the compounds, which can itself be viewed as a control, a buffer only control was used (page 38, line 16). It would be clear to the skilled artisan reviewing this disclosure that a suitable control for the identification of putative ligands for orphan GPCRs as covered by claim 43 would be to measure GPCR activity in the presence and absence of potential ligands.

With regard to the embodiment of claim 64, the specification at page 9, lines 2-4 states that “it may be desirable to compare activation of the CNG channel in the presence of the agent to activation of the channel in the absence of the agent.” As further disclosed at page 25, lines 13-15, the ability of a known ligand to induce GPCR activity may be assayed in the presence of

an agent. It would be clear to the skilled artisan reading this disclosure that identification of putative GPCR modulatory agents as covered by claim 64 may be performed in the absence of the putative agent as a control.

In light of the above, new claims 103, 104, and 105 have been added that are directed to the controls disclosed in the specification. Nevertheless, Applicants respectfully submit that the claimed methods are fully enabled by the specification and in light of the state of the art at the time of filing.

Further, Applicants herein submit an expert declaration according to 37 C.F.R. § 1.132 solely in an effort to further prosecution. Applicants respectfully request that the Examiner reconsider and withdraw this ground for rejection.

In addition, the Examiner alleges that claims 22-24, 26, 28-41, 43-45, 47, 49-62, 64-67, 69, 71, and 73-82 are not enabling for the use of a membrane potential dye that does not produce a fluorescent signal in response to cell depolarization. Without agreeing with the rejection and solely in an effort to expedite allowance, claims 22, 43, and 64 have been amended to include the limitation “that produces a fluorescent signal in response to cell depolarization.” Written support for this amendment can be found on page 23, lines 10-14. This ground for the rejection is therefore moot.

Rejection of claims 22-24, 26, 28-41, 43-45, 47, 49-62, 64-67, 69, 71, and 73-82 under 35 U.S.C. §112, second paragraph

In the Office Action, claims 22-24, 26, 28-41, 43-45, 47, 49-62, 64-67, 69, 71, and 73-82 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for

failing to point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges claims 22-24, 26, 28-41, 43-45, 47, 49-62, 64-67, 69, 71, and 73-82 are vague and indefinite because there is no antecedent basis for “detectable fluorescence signals from the dye.” Claims 22, 43, and 64 have been amended to include the limitation that the dye “produces a fluorescent signal” which serves as antecedent basis for “detectable fluorescence signals from the dye.” This ground for rejection is therefore moot.

The Examiner asserts that claims 39, 60, and 82 are confusing because the relationship between the “promiscuous G protein” and the “G protein-coupled receptor” is allegedly not specified. Applicants respectfully disagree and assert that the relationship between a promiscuous G protein and a G protein-coupled receptor is well known by one of ordinary skill in the art. For instance, the specification of the present application provides on page 25, lines 20-29 and page 21, lines 3-4, that a promiscuous G protein can act as a universal adapter and, when activated by a GPCR partner, results in calcium mobilization. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this ground for rejection.

Finally, the Examiner asserts that claims 41 and 62 are confusing because it is unclear if the limitation “a dye” is referring to the “at least one membrane potential dye” or an additional dye of unspecified function. Claims 41 and 62 have been amended to read “the dye.” This ground for rejection is therefore moot.

Conclusion

This reply is fully responsive to the Office Action dated June 13, 2005. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, he is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully Submitted,
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